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Bis-14-membered ring diketal diamines: Synthesis and evaluation of their anti-HIV and anti-tumoral activities

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Abstract

Chiral and achiral macrocyclic bis-diketal diamines, analogs of bicyclam AMD 3100, were synthesized in three steps from the previously obtained 14-membered ring diketal dilactams. Their monoreduction with lithium aluminium hydride gave the corresponding diketal aminolactams. Coupling these with dibromo-*p*-xylene led to xylyl dimer compounds. A second reduction step yielded the expected bis-diketal diamines in the methyl and unsubstituted series. Biological tests on the unreduced and reduced dimers showed both weak anti-HIV and anti-proliferative activities for the bis-diphenyl diketal aminolactam **13b**, with a mode of action probably different from that of AMD 3100.

1. Introduction

Macrocyclic saturated polyamines have generated continuous interest because of their physicochemical and biological properties [1]. Among these derivatives, bicyclams form a new class of compounds that exhibit anti-viral [1b, 2-7] and anti-tumoral [7-9] activities as antagonists of the chemokine co-receptor CXCR4 of the cell membrane [3-9]. As anti-HIV-1 agents, they interfere at the virus-cell fusion step in blocking the interaction between CXCR4 and the glycoproteins gp 120 of the viral envelope, i.e. the entry of the virus into the host cell, and thereby its replication [3-7]. As anti-tumoral agents, they block the binding of CXCR4 with its natural ligand, the chemokine C-X-C, SDF-1 α (stromal cell-derived factor), and hence inhibit growth, migration and proliferation of cancerous cells [7-9]. One of these compounds, the xylyl bicyclam AMD 3100, several synthesis of which have been reported [2b, 3c,10], has so far proved to be the most specific CXCR4 antagonist with a nanomolar binding affinity [2a, 3a, 4c, 5-7]. However, this molecule presents poor oral bioavailability due to its highly polar nature [5-6], and possible cardiac side effects disclosed after Phase II trials [6]. In this light, novel chemical analogs of this bioactive agent were likely to be of interest.

In continuation of our work on the synthesis, conformational analysis and binding properties of new macrocyclic 14-membered ring diketal dilactams [11], and diketal diamines [12], we report the synthesis of substituted bis-dioxygenated analogs of bicyclam AMD 3100 (Fig. 1) and the evaluation of their anti-viral and anti-tumoral activities.

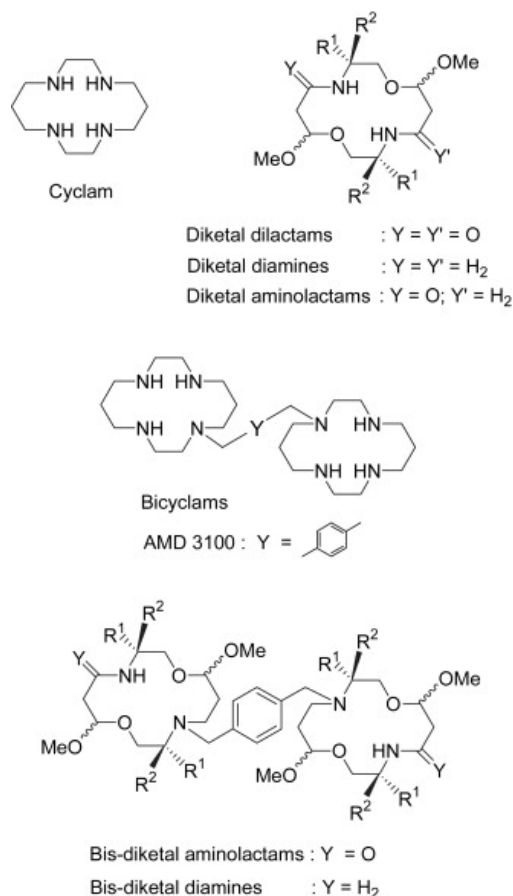


Fig. 1. General structure of cyclam, diketal dilactams, diketal diamines, diketal aminolactams, bicyclams, bis-diketal dilactams, and bis-diketal diamines.

2. Chemistry

2.1. Synthesis

Bis-diketal diamines were targeted by a coupling reaction of diketal aminolactams (Fig. 1), previously obtained as minor products in the synthesis of diketal diamines by reduction of the corresponding diketal dilactams [12].

2.1.1. Synthesis of diketal aminolactams

The study was conducted on the two major isomers **b** (*trans*-OMe) and **c** (*cis*-OMe) [13] of the three already developed series of diketal dilactams (**1**: $R^1 = Ph$, $R^2 = H$; **2**: $R^1 = H$, $R^2 = Me$; **3**: $R^1 = R^2 = H$), using lithium aluminium hydride (10 equiv.) as reducing agent [12]. However, some modifications were made to the previously described reaction conditions to invert the ratio of singly reduced compounds **4–6** to doubly reduced compounds **7–9** (Fig. 2, Table 1). As previously, small amounts of NEt_3 were added to minimize the effect of an elimination side reaction leading to unsaturated ketal aminolactams **10–12** [12].

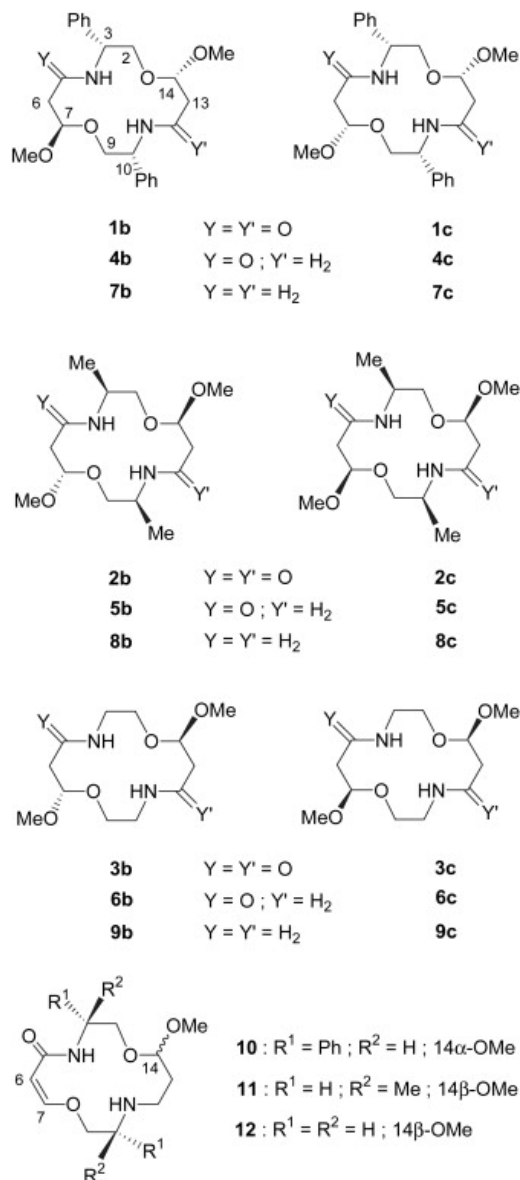


Fig. 2. Structure and stereochemistry of compounds **1b,c**, **9b,c**, **10–12**.

Table 1.

Reduction of diketal dilactams **1b,c**, **2b,c** and **3b,c** by LAH (10 equiv) in THF, and in the presence of small amounts of NEt₃ (0.1–0.2 equiv.).

Entry	Substrate (R)	$c_{\text{substrate}}$ (10 ⁻³ M)	Time (h)	Conv. (%) ^d	Results ^e (%)
1 ^a	1c (Ph)	17	9	90	4c (16), 7c (21), 10 (14)
2 ^b	1c (Ph)	25	11	95	4c (8), 7c (30), 10 (8)
3	1c (Ph)	8	9	84	4c (35), 7c (10), 10 (8)
4	1b (Ph)	14	10	85	4b (48), 7b (4)
5	2b (Me)	12	18	93	5b (21), 8b (20), 11 (2)
6	2b (Me)	8	18	88	5b (28), 8b (12), 11 (2)
7	2c (Me)	10	20	85	8c (17)
8	2c (Me)	5	20	85	5c (1), 8c (12)
9 ^c	2c (Me)	4	9	60	5c (12), 8c (22), 11 (1)
10	3b (H)	5	9	78	6b (27), 9b (16), 12 (2)

Entry	Substrate (R)	$c_{\text{substrate}}$ (10^{-3} M)	Time (h)	Conv. (%) ^d	Results ^e (%)
11	3c (H)	3	10	70	6c (29), 9c (14)

^a Absence of NEt₃.

^b Molar ratio of NEt₃/substrate = 0.4/1.

^c Molar ratio of LAH/substrate = 6:1.

^d Conversion rate based on the amount of recovered starting material.

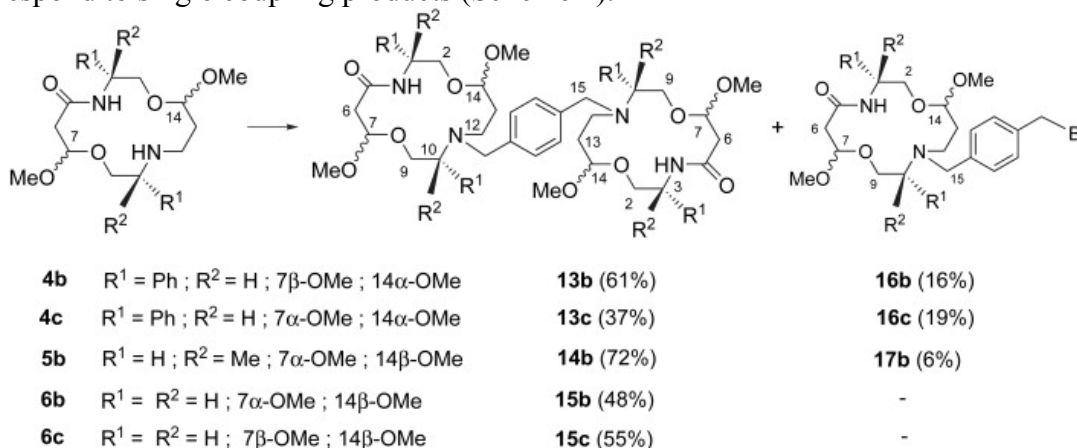
^e Isolated yield by column chromatography; at the end of the process, unidentified polar compounds were invariably isolated in 7–22% yield, which increased with the reaction time.

Comparison of entries 1 and 2 (Table 1), which recall two earlier experiments carried out from phenyl diketal dilactam **1c** [12a], showed that a lower substrate concentration favoured the formation of diketal aminolactam **4c**, the yield of which could be optimized in the conditions of entry 3. Entry 4 reports the optimal formation conditions of both diketal aminolactam **4b** and diketal diamine **7b**, the reaction always leading mainly to the mono-reduced compound independently of the concentration [12b]. In the methyl series, a better yield of aminolactam **5b** was obtained in the conditions of entry 6 ($c = 8 \times 10^{-3}$ M) compared with the previously reported conditions of entry 5 [12b]. In contrast, the formation of **5c** was only perceptible (yield 12%, conversion rate 60%) on decreasing the excess of LAH (6 equiv.) and the reaction time (9 h) (entry 9 compared with entries 7 and 8). In the unsubstituted series the best formation conditions of diketal aminolactams **6b** and **6c** were found at concentrations 5×10^{-3} M and 3×10^{-3} M respectively, using 10 equiv. of LAH (entries 10 and 11).

As previously reported [12], in all the series the reduction occurred with moderate total yields (43–53% for the selected entries) that were difficult to improve. These results may be explained by the presence of polar compounds (Table 1) probably resulting from complexation between the diketal diamines generated and the Li⁺ cation, which could therefore no longer catalyse the reaction [14].

2.1.2. Synthesis of bis-diketal aminolactams

The coupling step between diketal aminolactams **4–6** and the α,α' -dibromo-*p*-xylene was studied from the substrates obtained in appreciable yields, i.e. from **4b,c**, **5b**, **6b,c**. The reactions were performed with minor variations of literature procedures [2b,3c,10], using K₂CO₃ as basic agent [2b,3c]. They led to the expected bis-diketal aminolactams **13–15**, obtained in moderate to good yields (37–72%), and accompanied in both substituted series by small amounts (6–19%) of bromo ketal aminolactams **16–17**, which correspond to single coupling products (Scheme 1).



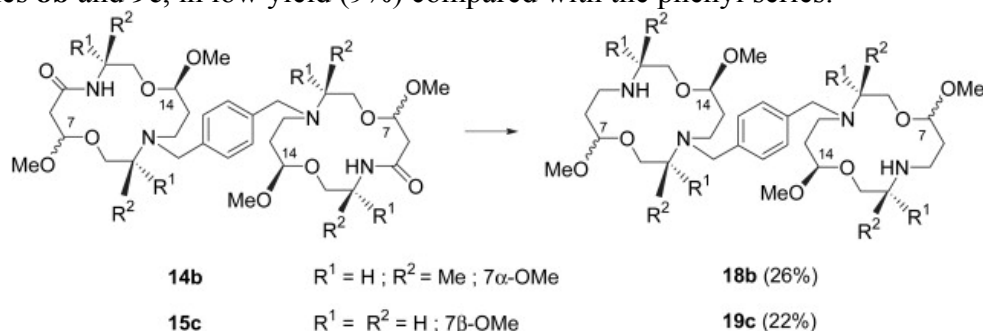
Scheme 1. Reagents and conditions: α,α' -dibromo-*p*-xylene (0.5–0.6 equiv.), K₂CO₃ (1.0–1.2 equiv.), CH₃CN ($c_{\text{substrate}} = 50 \times 10^{-3}$ M), Δ , 8–10 h.

2.1.3. Synthesis of bis-diketal diamines

Due to the moderate yields of **13c** and **15b**, the reduction of bis-diketal aminolactams was studied on only **13b**, **14b** and **15c**, i.e. on the isomer of each series obtained with the best yield. The reactions were repeated with LAH (10 equiv.) in THF and in the presence of NEt₃ (0.02 equiv./LAH). An inverse addition order of the reactants, namely the addition of a commercial THF hydride solution to the substrate solution, was adopted due to the small amounts of starting materials available.

In the phenyl series, the reduction performed at different substrate concentrations and reaction times led to either an incomplete reaction giving rise to a mixture of singly and doubly reduced bis-macrocycles difficult to separate ($c_{\text{substrate}} = 30 \times 10^{-3}$ M, 10 h and 40×10^{-3} M, 9 h), or a major cleavage reaction regenerating diphenyl diketal diamine **7b** ($c_{\text{substrate}} = 50$ and 60×10^{-3} M, 8 h).

In contrast, in the methyl and unsaturated series, diketal diamines **18b** and **19c** were obtained with 26% and 22% yields respectively (conversion rate 100%) with the following substrate concentrations and reaction times: **18b**, $c_{\text{substrate}} = 100 \times 10^{-3}$ M, 9 h; **19c**, $c_{\text{substrate}} = 60 \times 10^{-3}$ M, 6 h (Scheme 2). In both cases, the reduction was also partially accompanied by a benzyl cleavage giving rise to the corresponding diketal diamines **8b** and **9c**, in low yield (9%) compared with the phenyl series.



Scheme 2. Reagents and conditions: LAH (10 equiv.), NEt_3 (0.2 equiv.), THF ($c_{\text{substrate}} = 60\text{--}100 \times 10^{-3}$ M), Δ , 6–9 h.

In summary, the access to bis-diketals succeeded in the methyl and unsubstituted series but failed in the phenyl series. The difficulties observed in the reduction of the bis-phenyl aminolactam **13b**, in which the 3,3'-Ph, and 7,7'-OMe groups are in a *trans* position, are probably due to the hindrance of the two faces of the molecule at the level of the 5,5'-CO carbonyl groups, as previously reported in the reduction of *trans*-OMe phenyl diketal dilactam **1b** [12b]. In the two successful series, the reduction took place again with moderate total yields (30–35%) which were difficult to improve as in the formation of compounds **4–9** above.

2.2. Characterization

The structure and stereochemistry of all the derivatives **4–19** were established from IR, MS, 1D NMR [^1H , ^{13}C (J MOD)] and 2D NMR [COSY 1H-1H, HSQC (heteronuclear single quantum correlation) and sometimes HMBC (heteronuclear multiple bond correlation)] spectroscopic data, which allowed identification of all the hydrogen and carbon atoms.

The characteristics of the monomer compounds **4–12** have already been reported [12b]. Briefly, (i) in the ^1H and ^{13}C NMR spectra, diamines **7c**, **8c**, **9b,c**, which all possess a symmetry element (C_2 for **7c**, **8c**, **9c**, center for **9b**), show only one signal for each pair of identical groups of the macrocycle, whereas diamines **7b** and **8b** exhibit double signals due to the asymmetry of the two ring chains, and (ii) the reduced carbonyl of *trans*-OMe aminolactams **4b** and **5b** correspond to the 12-CO carbonyl of chain 2 in which the 14-OMe group and the 3,10-*R* substituents are in a *cis* position [12b].

The ^1H and ^{13}C NMR spectra of the dimer compounds **13–19** are also simplified due to the presence of a C_2 axis perpendicular to the aromatic linker.

3. Biological assays

Anti-HIV and anti-tumoral tests were performed on the two synthesized bis-diketals **18b**, **19c**, and on the three bis-diketals aminolactams **13b,c**, **15b**, not involved in the last reduction step.

3.1. Anti-HIV activity evaluation

Since the anti-HIV activity of AMD 3100 appears to be confined to the T-lymphotropic (X4) HIV strains, i.e. those strains that use the CXCR4 receptor to enter their target cells [7b], the effects of the above chemical entities were studied *in vitro* with two T cell lines, MT-4 and CEM-SS, infected by X4 viral isolates. The activity of a given compound on the replication of HIV-1 was measured by quantification of (i) the inhibition of virus-induced cytopathogenicity in infected MT-4 cells, and (ii) the reverse transcriptase (RT) activity associated with virus particles released from infected CEM-SS cells.

The 50% cytotoxic concentration (CC₅₀) was evaluated in parallel to the 50% inhibitory concentration (IC₅₀) (Table 2). Among the tested compounds, only the bis-diphenyl diketal aminolactam **13b** showed an inhibitory activity in regard to HIV-1 infection in CEM-SS cells, but with lower values than AMD 3100. Table 2.

Anti-viral activity and cytotoxicity data of bis-diketal aminolactams **13b,c**, **15b**, and bis-diketal diamines **18b**, **19c**, evaluated on MT-4 cells and on CEM-SS cells infected with X4 HIV strains (HIV-1IIB and HIV-1 LAI respectively).^a

Compound (R)	HIV-1 IIB/MT4		HIV-1 LAI/CEM-SS	
	IC ₅₀ ^b (μM)	CC ₅₀ ^c (μM)	IC ₅₀ ^b (μM)	CC ₅₀ ^c (μM)
13b (Ph)	>CC ₅₀	7.8	8.65	>10
13c (Ph)	>10	>10	>10	>10
15b (H)	>100	>100	>100	>100
18b (Me)	>100	>100	>100	>100
19c (H)	> CC ₅₀	50	>50	>50
AMD 3100 ^d	0.41	6.5	0.32	>5

^a All data represent mean values of 2 separate experiments.

^b IC₅₀: 50% inhibitory concentration = concentration needed to inhibit 50% virus replication *in vitro*.

^c CC₅₀: 50% cytotoxic concentration = concentration required to cause 50% death of uninfected cells.

^d Commercial sample purchased from CheMatech.

3.2. Anti-tumoral activity evaluation [15]

The *in vitro* anti-proliferative activities of compounds **13b,c**, **15b**, **18b** and **19c** were evaluated in triplicate towards ten human cell lines [buccal carcinoma (KB), glioblastoma (SF268), myeloid leukaemia (HL60), mammary carcinoma (MCF7 and MCF7R), colon carcinoma (HCT116), pulmonary carcinoma (A549), prostate adenocarcinoma (PC3), ovary adenocarcinoma (OV3) and hepatocarcinoma (HepG2)] using the classic colorimetric MTS test (Table 3). Taxotere was used as a positive control at a drug concentration of 2.5×10^{-10} M. The percentage of cell proliferation inhibition was defined as absorbance in experimental wells compared with absorbance in control wells, after subtraction of the blank values. Under the conditions used (10^{-5} M final concentration of tested compounds), the bis-diphenyl diketal aminolactam **13b** showed a mild cytotoxic activity of about 50% towards five cell lines (KB, HL60, MCF7, HCT116 and PC3), i.e. a cytotoxicity corresponding approximately to an IC₅₀ of ≈ 10 μM.

Table 3.

Percentage cell proliferation inhibition of bis-diketal aminolactams **13b,c**, **15b**, and bis-diketal diamines **18b**, **19c**, at a drug concentration of 10^{-5} M.^a

Compound	KB	SF268	HL60	MCF7	MCF7R	HCT116	A549	PC3	OV3	HepG2
13b ^b	47	27	54	45	14	47	33	51	38	27
13c	12	14	31	25	08	21	17	15	18	00
15b	00	00	10	13	02	07	00	00	00	04
18b	11	05	08	00	04	10	00	09	08	00
19c	00	12	08	08	04	11	00	10	15	00
Taxotere ^c	75	37	19	0	0.03	24	14	9	22	0

^a All experiments were carried out in triplicate with DMSO as solvent.

^b For **13b**, the best observed values ($\approx 50\%$) correspond approximately to an IC₅₀ ≈ 10 μM.

^c Data from Ref. [15]. Taxotere was used as a positive control at a drug concentration of 2.5×10^{-10} M.

4. Discussion

Biological tests, performed on the synthesized bis-macrocyclic compounds **13b,c**, **15b**, **18b**, **19c** gave an encouraging result for one analog compared with the others: bis-phenyl diketal aminolactam **13b** showed both a weak anti-HIV-1 activity and some anti-proliferative effects. The interaction of AMD 3100 with the receptor CXCR4 has been described as probably due to binding of two antiperiplanar NH amine functions of the two cyclam moieties with the free carboxylic acid groups of Asp171 and Asp262 located on respectively transmembrane TM-IV and TM-VI of the receptor [4b,6b,7]. This is not possible in **13b** since the two NH concerned are involved in amide links. Hence the activity of this compound probably depends on other factors e.g. π - π stacking effects between the 3,3',10,10'-phenyl substituents of the molecule and aromatic rings of Phe, Tyr and (or) Trp units of the transmembrane.

5. Conclusion

Variously substituted bis-diketal aminolactams and bis-diketal diamines were prepared in two and three steps respectively from previously and rapidly synthesized macrocyclic diketal dilactams [11a]. The first step, which corresponded to the formation of singly reduced compounds **4–6**, was efficient in a $3\text{--}14 \times 10^{-3}$ M concentration range for five of the six series, but failed from the *cis* methyl dilactam **2c**, the reduction of which led mainly to diamine **8c**, irrespective of the concentration. After a coupling stage which gave bis-diketal aminolactams **13–15** in 37–72% yield, the final reduction step allowed the isolation of bis-diketal diamines **18b** (R = Me) and **19c** (R = H), while a partial reaction or a major benzyl cleavage accompanied the reduction of the phenyl product **13b**.

Biological assays made on the unreduced and reduced dimer macrocycles showed that the bis-diphenyl diketal aminolactam **13b** was the most promising compound, with both weak anti-HIV and anti-proliferative activities. These results lead to consider a mode of action different from that of AMD 3100, and indicate the probable importance of phenyl groups susceptible to induce π - π stacking effects with aromatic units of the CXCR4 receptor. The development and biological evaluation of new analogs incorporating phenyl substituents would enable us to test this hypothesis.

6. Experimental

6.1. Chemistry

6.1.1. General remarks

Solvents were obtained dried as follows: tetrahydrofuran (THF) was distilled from benzophenone ketyl, CH_2Cl_2 and CH_3CN were refluxed over and distilled from CaH_2 , CH_3OH was distilled from magnesium. The organic layers were dried with MgSO_4 . Reactions were monitored by thin layer chromatography (TLC) on aluminium plates precoated with silica gel (Merck 60 F₂₅₄) and spots visualized by UV light or by spraying with a ceric sulphate and ammonium molybdate acid solution. Flash chromatography was carried out with silica gel (Merck 0.040–0.063 mm). Optical rotations were measured at the sodium D line (589 nm) using a 1 dm quartz cell with a JASCO DIP-370 apparatus. IR spectra were scanned with a Perkin–Elmer 881 spectrophotometer (ν_{max} in cm^{-1}). 1D (^1H and ^{13}C -J MOD) and 2D (COSY ^1H - ^1H , HSQC ^1H - ^{13}C) NMR spectra were recorded with a Bruker Avance 400 spectrometer equipped with a $^1\text{H}/^{13}\text{C}$ probe (^1H : 400 MHz; ^{13}C : 100 MHz), and 2D HMBC ^1H - ^{13}C NMR spectra with an Avance 500 apparatus long dist 7.7 Hz (^1H : 500 MHz; ^{13}C : 125 MHz). Chemical shifts δ were noted in parts per million (ppm) and splitting patterns designated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doubled doublet (dd), doublet of doublet of doublet (ddd), doubled triplet (dt), multiplet (m), broad signal (br. s). The solvent (CDCl_3) was taken as internal reference [$\delta = 7.27$ ppm for ^1H NMR and 77.1 ppm (central line) for ^{13}C NMR]. Proton and carbon atoms were assigned according to the numbering indicated in Fig. 2 and Scheme 1. Mass spectra were recorded with either an HP 5989B (CI) or a micro Q-TOF Waters (ESI) apparatus.

6.1.2. Diketal aminolactams: general procedure

To a suspension of LiAlH₄ (10 equiv.) in dry THF (0.5 mL for 1 mmol of LAH) was added NEt₃ (0.01–0.04 equiv./LAH), and dropwise a solution of diketal dilactam (1 equiv.) in dry THF ($c_{\text{substrate}} = 3\text{--}14 \times 10^{-3}$ M). The reaction mixture was heated at reflux while stirring for 9–18 h. Excess hydride was destroyed by adding H₂O (10 equiv./LAH). The precipitates were filtered and washed with THF and CH₂Cl₂. The organic layer was dried with MgSO₄ and evaporated in vacuo. Purification by flash chromatography (silicagel, Et₂O/MeOH) yielded diketal aminolactams and diketal diamines.

6.1.2.1. (3*R*,7*R*,10*R*,14*S*)-Diphenyl diketal aminolactam (4b), (3*R*,7*R*,10*R*,14*S*)-diphenyl diketal diamine (7b)

The preparation of these compounds was described previously [12b].

6.1.2.2. (3*R*,7*S*,10*R*,14*S*)-Diphenyl diketal aminolactam (4c), (3*R*,7*S*,10*R*,14*S*)-diphenyl diketal diamine (7c), and (3*R*,10*R*,14*S*)-diphenyl unsaturated ketal aminolactam (10)

These compounds were prepared from diphenyl diketal dilactam **1c** (66.4 mg, 0.15 mmol), LiAlH₄ (57 mg, 1.5 mmol, 10 equiv.), NEt₃ (1 M solution in THF, 30 μ L, 30 μ mol, 0.02 equiv./LAH), and THF (19 mL, $c_{\text{substrate}} = 8.0 \times 10^{-3}$ M) according to the general procedure (reaction time 9 h). Excess hydride was destroyed by adding H₂O (270 μ L, 15 mmol). Chromatography (Et₂O/MeOH, gradient 100:0–60:40) afforded diketal aminolactam **4c** (18.9 mg, 44 μ mol, 35%), diketal diamine **7c** (5.2 mg, 12.6 μ mol, 10%) and unsaturated ketal aminolactam **10** (4.0 mg, 10.1 μ mol, 8%) with 84% conversion rate. Data of **4c**, **7c**, and **10** were given previously [12a].

6.1.2.3. (3*S*,7*S*,10*S*,14*R*)-Dimethyl diketal aminolactam (5b), (3*S*,7*S*,10*S*,14*R*)-dimethyl diketal diamine (8b), and (3*S*,10*S*,14*R*)-dimethyl unsaturated ketal aminolactam (11)

These compounds were prepared from methyl diketal dilactam **2b** (63.7 mg, 0.20 mmol), LiAlH₄ (76 mg, 2.0 mmol, 10 equiv.), NEt₃ (1 M solution in THF, 20 μ L, 20 μ mol, 0.01 equiv./LAH), and THF (25 mL, $c_{\text{substrate}} = 8.0 \times 10^{-3}$ M) according to the general procedure (reaction time 18 h). Excess hydride was destroyed by adding H₂O (360 μ L, 20 mmol). Chromatography (Et₂O/MeOH, gradient 100:0–0:100) afforded diketal aminolactam **5b** (15.0 mg, 49.3 μ mol, 28%), diketal diamine **8b** (6.1 mg, 21.1 μ mol, 12%) and unsaturated ketal aminolactam **11** (0.9 mg, 3.5 μ mol, 2%) with 88% conversion rate. Data of **5b**, **8b**, and **11** were given previously [12b].

6.1.2.4. (3*S*,7*R*,10*S*,14*R*)-Dimethyl diketal aminolactam (5c), (3*S*,7*R*,10*S*,14*R*)-dimethyl diketal diamine (8c) and (3*S*,10*S*,14*R*)-dimethyl unsaturated ketal aminolactam (11)

These compounds were prepared from methyl diketal dilactam **2c** (63.7 mg, 0.20 mmol), LiAlH₄ (45.5 mg, 1.2 mmol, 6 equiv.), NEt₃ (1 M solution in THF, 12 μ L, 12 μ mol, 0.01 equiv./LAH), and THF (50 mL, $c_{\text{substrate}} = 4.0 \times 10^{-3}$ M) according to the general procedure (reaction time 9 h). Excess hydride was destroyed by adding H₂O (216 μ L, 12 mmol). Chromatography (Et₂O/MeOH, gradient 100:0–0:100) afforded diketal aminolactam **5c** (4.4 mg, 14.4 μ mol, 12%), diketal diamine **8c** (7.7 mg, 26.4 μ mol, 22%) and unsaturated ketal aminolactam **11** (0.3 mg, 1.2 μ mol, 1%) with 60% conversion rate. Data of **5c**, **8c**, and **11** were given previously [12b].

6.1.2.5. (7*S,14*R**)-Diketal aminolactam (6b), (7*S**,14*R**)-diketal diamine (9b), and 14*R**-unsaturated ketal aminolactam (12)**

These compounds were prepared from diketal dilactam **3b** (72.6 mg, 0.25 mmol), LiAlH₄ (95 mg, 2.5 mmol, 10 equiv.), NEt₃ (1 M solution in THF, 50 μ L, 50 μ mol, 0.02 equiv./LAH), and THF (50 mL, $c_{\text{substrate}} = 5.0 \times 10^{-3}$ M) according to the general procedure (reaction time 9 h). Excess hydride was destroyed by adding H₂O (450 μ L, 25 mmol). Chromatography (Et₂O/MeOH, gradient 100:0–0:100) afforded diketal aminolactam **6b** (14.5 mg, 52.6 μ mol, 27%), diketal diamine **9b** (8.2 mg, 31.2 μ mol, 16%) and unsaturated ketal aminolactam **12** (1.0 mg, 4.0 μ mol, 2%) with 78% conversion rate.

Data for **6b**: $R_f = 0.50$ (MeOH/NH₄OH: 99.5/0.5, 2 elutions). IR (CHCl₃): ν_{max} 3450, 3420, 3340 (NH); 1660 (CO). ¹H NMR and COSY ¹H-¹H (400 MHz, CDCl₃): δ_{H} 1.89 (dddd, 1H, H-13B, ² $J = 14.5$ Hz, ³ $J = 7.6, 2.7, 2.4$ Hz), 1.99 (dddd, 1H, H-13A, ² $J = 14.5$ Hz, ³ $J = 8.7, 8.1, 2.8$ Hz), 2.53 (dd, 1H, H-6B, ² $J = 14.6$ Hz, ³ $J = 1.9$ Hz), 2.56 (br. s, 1H, NH amine), 2.70 (dd, 1H, H-6A, ² $J = 14.6$ Hz, ³ $J = 8.6$ Hz),

2.75 (ddd, 1H, H-12B, $^2J = 11.5$ Hz, $^3J = 8.7$, 2.7 Hz), 2.81 (ddd, 1H, H-10B, $^2J = 12.6$ Hz, $^3J = 5.3$, 2.6 Hz), 2.89 (ddd, 1H, H-12A, $^2J = 11.5$ Hz, $^3J = 7.6$, 2.8 Hz), 2.91 (ddd, 1H, H-10A, $^2J = 12.6$ Hz, $^3J = 8.5$, 2.8 Hz), 3.33 (s, 3H, OCH₃), 3.36 (s, 3H, OCH₃), 3.38 (dddd, 1H, H-3B, $^2J = 13.7$, $^3J = 6.4$, 5.2, 2.4 Hz), 3.51 (ddd, 1H, H-2B, $^2J = 9.9$ Hz, $^3J = 7.9$, 2.4 Hz), 3.55 (ddd, 1H, H-9B, $^2J = 9.9$ Hz, $^3J = 8.5$, 2.6 Hz), 3.63 (dddd, 1H, H-3A, $^2J = 13.7$ Hz, $^3J = 7.9$, 5.6, 2.6 Hz), 3.82 (ddd, 1H, H-2A, $^2J = 9.9$ Hz, $^3J = 6.4$, 2.6 Hz), 3.96 (ddd, 1H, H-9A, $^2J = 9.9$ Hz, $^3J = 5.3$, 2.8 Hz), 4.62 (dd, 1H, H-14, $^2J = 8.1$, 2.4 Hz), 4.80 (dd, 1H, H-7, $^3J = 8.6$, 1.9 Hz), 7.00 (br. s, 1H, NH lactam). ¹³C NMR and HSQC (100 MHz, CDCl₃): δ_C 31.6 (C-13), 39.3 (C-3), 41.1 (C-6), 45.7 (C-12), 49.3 (C-10), 53.1 (OCH₃), 53.6 (OCH₃), 64.1 (C-2), 65.3 (C-9), 101.2 (C-7), 104.0 (C-14), 169.0 (CO). MS (ESI⁺): *m/z* (%) 299 (28) [M + Na]⁺, 277 (100) [M + H]⁺, 245 (87) [M + H-CH₃OH]⁺. HRMS (ESI⁺): calcd. for C₁₂H₂₅N₂O₅ [M + H]⁺ 277.1763, found 277.1767.

Data of **9b** were given previously [12b].

Data for **12**: *R_f* = 0.60 (MeOH, 3 elutions). IR (CHCl₃): ν_{\max} 3429 (NH), 1663 (CO), 1604 (C=C). ¹H NMR and COSY ¹H-¹H (400 MHz, CDCl₃): δ_H 1.60 (br. s, 1H, NH amine), 1.82 (dddd, 1H, H-13B, $^2J = 14.3$ Hz, $^3J = 7.2$, 2.2, 2.1 Hz), 1.99 (dddd, 1H, H-13A, $^2J = 14.3$ Hz, $^3J = 9.3$, 8.5, 2.3 Hz), 2.70 (ddd, 1H, H-12B, $^2J = 11.5$, $^3J = 9.3$, 2.1 Hz), 2.88 (m, 3H, H-10A, H-10B, H-12A), 3.28 (dddd, 1H, H-3B, $^2J = 11.0$, $^3J = 9.0$, 3.5, 2.5 Hz), 3.33 (s, 3H, OCH₃), 3.47 (td, 1H, H-2B, $^2J = 10.0$, $^3J = 2.5$ Hz), 3.85 (ddt, 1H, H-3A, $^2J = 11.0$, $^3J = 10.0$, 3.5 Hz), 3.91 (dt, 1H, H-2A, $^2J = 10.0$, $^3J = 3.5$ Hz), 4.07 (ddd, 1H, H-9B, $^2J = 10.3$, $^3J = 4.3$, 4.1 Hz), 4.21 (ddd, 1H, H-9A, $^2J = 10.3$, $^3J = 5.9$, 4.9 Hz), 4.58 (dd, 1H, H-14, $^3J = 8.5$, 2.2 Hz), 5.01 (d, 1H, H-6, $^3J = 6.9$ Hz), 6.48 (d, 1H, H-7, $^3J = 6.9$ Hz), 7.60 (br. s, 1H, NH lactam). MS (ESI⁺): *m/z* (%) 267 (100) [M + Na]⁺, 245 (52) [M + H]⁺, 213 (98) [M + H-CH₃OH]⁺. HRMS (ESI⁺): calcd. for C₁₁H₂₁N₂O₄ [M + H]⁺ 245.1501, found 245.1514.

6.1.2.6. (7*R**,14*R**)-Diketal aminolactam (**6c**) and (7*R**,14*R**)-diketal diamine (**9c**)

These compounds were prepared from methyl diketal dilactam **3c** (116.1 mg, 0.40 mmol), LiAlH₄ (152 mg, 4.0 mmol, 10 equiv.), NEt₃ (1 M solution in THF, 80 μ L, 80 μ mol, 0.02 equiv./LAH), and THF (133 mL, *c*_{substrate} = 3.0×10^{-3} M) according to the general procedure (reaction time 10 h). Excess hydride was destroyed by adding H₂O (720 μ L, 40 mmol). Chromatography (Et₂O/MeOH, gradient 100:0–0:100) afforded diketal aminolactam **6c** (22.5 mg, 81.4 μ mol, 29%) and diketal diamine **9c** (10.3 mg, 39.3 μ mol, 14%) with 70% conversion rate. Data of **6c** and **9c** were given previously [12b].

6.1.3. Bis-diketal aminolactams: general procedure

A suspension of diketal aminolactam, α,α' -dibromo-*p*-xylene (0.5–0.6 equiv.) and K₂CO₃ (1.0–1.2 equiv.) in dry CH₃CN (*c*_{substrate} = 50×10^{-3} M) was heated at reflux while stirring for 8–9 h. After evaporation of the solvent, the residue was dissolved in CH₂Cl₂. The precipitate was filtered and washed with CH₂Cl₂. The organic layer was dried with Mg₂SO₄ and evaporated in vacuo. Purification by flash chromatography (silica gel, Et₂O/MeOH) yielded bis-diketal aminolactams and small amounts of bromo diketal aminolactams.

6.1.3.1. Bis-(3*R*,7*R*,10*R*,14*S*)-diphenyl diketal aminolactam (**13b**) and (3*R*,7*R*,10*R*,14*S*)-bromoxylyl diphenyl diketal aminolactam (**16b**)

These compounds were prepared from diphenyl diketal aminolactam **4b** (25.7 mg, 60.0 μ mol), α,α' -dibromo-*p*-xylene (7.9 mg, 30.0 μ mol, 0.5 equiv.), K₂CO₃ (8.3 mg, 60.0 μ mol, 1.0 equiv.), and CH₃CN (1.2 mL, *c*_{substrate} = 50×10^{-3} M) according to the general procedure (reaction time 8 h). Chromatography (Et₂O/MeOH, gradient: 100:0–50:50) afforded bis-diketal aminolactam **13b** (16.0 mg, 16.8 μ mol, 61%) and bromoxylyl diphenyl diketal aminolactam **16b** (5.4 mg, 8.8 μ mol, 16%) with 92% conversion rate.

Data for **13b**: *R_f* = 0.40 (Et₂O/MeOH, 98:2, 3 elutions). [α]_D²⁵ –68.0 (*c* 0.90, CHCl₃). IR (CHCl₃): ν_{\max} 3367 (NH), 1665 (CO). ¹H NMR and COSY ¹H-¹H (400 MHz, CDCl₃): δ_H 1.86 (m, 4H, 2H-13A, 2H-13B), 2.56 (dd, 2H, 2H-6B, $^2J = 16.1$ Hz, $^3J = 1.5$ Hz), 2.61 (dt, 2H, 2H-12B, $^2J = 12.8$ Hz, $^3J = 4.9$ Hz), 2.84 (dd, 2H, 2H-6A, $^2J = 16.1$ Hz, $^3J = 8.7$ Hz), 3.10 (s, 6H, 2 OCH₃), 3.16 (s, 6H, 2 OCH₃), 3.30 (d, 2H, 2H-15B, $^2J = 14.7$ Hz), 3.34 (m, 2H, 2H-12A), 3.76 (dd, 2H, 2H-2B, $^2J = 9.8$ Hz, $^3J = 3.2$ Hz), 3.80 (d, 2H, 2H-15A, $^2J = 14.7$ Hz), 3.92 (dd, 2H, 2H-9B, $^2J = 10.0$ Hz, $^3J = 2.2$ Hz), 3.97 (dd, 2H, 2H-10, $^3J = 7.3$, 2.2 Hz), 4.10 (dd, 2H, 2H-2A, $^2J = 9.8$ Hz, $^3J = 2.9$ Hz), 4.11 (dd, 2H, 2H-9A, $^2J = 10.0$ Hz,

$^3J = 7.3$ Hz), 4.79 (dd, 2H, 2H-7, $^3J = 8.7$, 1.5 Hz), 4.84 (t, 2H, 2H-14, $^3J = 5.3$ Hz), 5.28 (ddd, 2H, 2H-3, $^3J = 7.9$, 3.2, 2.9 Hz), 7.28–7.42 (m, 24H, 24 Ar-H), 7.90 (d, 2H, 2 NH lactam, $^3J = 7.9$ Hz). ^{13}C NMR and HSQC (100 MHz, CDCl_3): δ_{C} 31.1 (2C-13), 40.0 (2C-6), 44.7 (2C-12), 52.0 (2 OCH₃), 52.3 (2C-3), 53.4 (2CH₃), 53.5 (2C-15), 63.4 (2C-10), 66.4 (2C-9), 70.5 (2C-2), 100.1 (2C-7), 102.3 (2C-14), 126.7–129.4 (14 ArCH), 136.6 (2 ArC), 138.3 (2 ArC), 140.4 (2 ArC), 168.3 (2CO). MS (ESI⁺): m/z (%) 981 (21) $[\text{M} + \text{Na}]^+$, 959 (7) $[\text{M} + \text{H}]^+$, 451 (100) $[\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_5 + \text{Na}]^+$, 429 (84) $[\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_5 + \text{H}]^+$, 339 (42). HRMS (ESI⁺): calcd. for $\text{C}_{56}\text{H}_{71}\text{N}_4\text{O}_{10}$ $[\text{M} + \text{H}]^+$ 959.5170, found 959.5210.

Data for **16b**: $R_f = 0.60$ (Et₂O). $[\alpha]_{\text{D}}^{25} -56.6$ (c 0.57, CHCl_3). IR (CHCl_3) ν_{max} 3360 (NH), 1660 (CO). ^1H NMR and COSY ^1H - ^1H (400 MHz, CDCl_3): δ_{H} 1.85 (m, 2H, H-13A, H-13B), 2.55 (ddd, 1H, H-12B, $^2J = 11.8$ Hz, $^3J = 4.7$, 0.5 Hz), 2.57 (dd, 1H, H-6B, $^2J = 16.2$ Hz, $^3J = 1.6$ Hz), 2.83 (dd, 1H, H-6A, $^2J = 16.2$ Hz, $^3J = 8.7$ Hz), 3.11 (s, 3H, 7-OCH₃), 3.14 (s, 3H, 14-OCH₃), 3.31 (d, 1H, H-15B, $^2J = 15.0$ Hz), 3.32 (ddd, 1H, H-12A, $^2J = 11.8$ Hz, $^3J = 10.2$, 6.5 Hz), 3.74 (dd, 1H, H-2B, $^2J = 10.0$ Hz, $^3J = 3.3$ Hz), 3.79 (d, 1H, H-15A, $^2J = 15.0$ Hz), 3.89 (dd, 1H, H-9B, $^2J = 10.2$ Hz, $^3J = 2.6$ Hz), 3.96 (dd, 1H, H-10, $^3J = 8.4$, 2.6 Hz), 4.09 (dd, 1H, H-2A, $^2J = 10.0$ Hz, $^3J = 2.7$ Hz), 4.13 (dd, 1H, H-9A, $^2J = 10.2$ Hz, $^3J = 8.4$ Hz), 4.52 (s, 2H, CH₂Br), 4.78 (dd, 1H, H-14, $^3J = 5.9$, 5.3 Hz), 4.79 (dd, 1H, H-7, $^3J = 8.7$, 1.6 Hz), 5.27 (ddd, 1H, H-3, $^3J = 7.6$, 3.3, 2.7 Hz), 7.22–7.42 (m, 14H, 14 Ar-H), 7.90 (d, 1H, NH lactam, $^3J = 7.6$ Hz). ^{13}C NMR and HSQC (100 MHz, CDCl_3): δ_{C} 31.1 (C-13), 33.6 (CH₂Br), 40.1 (C-6), 44.4 (C-12), 52.1 (14-OCH₃), 52.2 (C-3), 53.2 (7-OCH₃), 53.4 (C-15), 63.6 (C-10), 66.3 (C-9), 70.6 (C-2), 100.0 (C-7), 102.3 (C-14), 127.0–129.4 (14 Ar-CH), 136.1 (Ar-C), 136.6 (Ar-C), 140.2 (Ar-C), 140.4 (Ar-C), 168.2 (CO). MS (ESI⁺): m/z (%) 635 (9) $[\text{M} + \text{Na} (^{81}\text{Br})]^+$, 633 (9) $[\text{M} + \text{Na} (^{79}\text{Br})]^+$, 613 (98) $[\text{M} + \text{H} (^{81}\text{Br})]^+$, 611 (100) $[\text{M} + \text{H} (^{79}\text{Br})]^+$, 555 (16), 553 (16). HRMS (ESI⁺): calcd. for $\text{C}_{32}\text{H}_{40}^{79}\text{BrN}_2\text{O}_5$ $[\text{M} + \text{H}]^+$ 611.2121, found 611.2132.

6.1.3.2. Bis-(3*R*,7*S*,10*R*,14*S*)-diphenyl diketal aminolactam (**13c**) and (3*R*,7*S*,10*R*,14*S*)-bromoxylyl diphenyl diketal aminolactam (**16c**)

These compounds were prepared from diphenyl diketal aminolactam **4c** (17.1 mg, 40.0 μmol), α,α' -dibromo-*p*-xylene (6.3 mg, 24.0 μmol , 0.6 equiv.), K₂CO₃ (6.6 mg, 48.0 μmol , 1.2 equiv.), and CH₃CN (0.8 mL, $c_{\text{substrate}} = 50 \times 10^{-3}$ M) according to the general procedure (reaction time 8 h). Chromatography (Et₂O/MeOH, gradient 100:0–50:50) afforded bis-diketal aminolactam **13c** (7.1 mg, 7.4 μmol , 37%) and bromoxylyl diphenyl diketal aminolactam **16c** (4.7 mg, 7.7 μmol , 19%) with 100% conversion rate.

Data for **13c**: $R_f = 0.33$ (Et₂O/MeOH, 98:2). $[\alpha]_{\text{D}}^{25} -56.1$ (c 0.25; CHCl_3). IR (CHCl_3): ν_{max} 3436 and 3372 (NH), 1666 (CO). ^1H NMR and COSY ^1H - ^1H (400 MHz, CDCl_3): δ_{H} 1.87 (q, 4H, 4H-13, $^3J = 6.4$ Hz), 2.59 (dd, 2H, 2H-6B, $^2J = 14.5$ Hz, $^3J = 2.4$ Hz), 2.63 (dd, 2H, 2H-6A, $^2J = 14.5$ Hz, $^3J = 7.0$ Hz), 2.76 (dt, 2H, 2H-12B, $^2J = 12.9$ Hz, $^3J = 6.4$ Hz), 3.11 (dt, 2H, 2H-12A, $^2J = 12.9$ Hz, $^3J = 6.4$ Hz), 3.19 (s, 12H, 4 OCH₃), 3.43 (d, 2H, 2H-15B, $^2J = 14.3$ Hz), 3.74 (d, 2H, 2H-15A, $^2J = 14.3$ Hz), 3.83 (dd, 2H, 2H-9B, $^2J = 10.3$ Hz, $^3J = 3.3$ Hz), 3.84 (dd, 2H, 2H-2B, $^2J = 10.8$ Hz, $^3J = 4.2$ Hz), 3.91 (dd, 2H, 2H-2A, $^2J = 10.8$ Hz, $^3J = 4.9$ Hz), 3.92 (dd, 2H, 2H-10, $^3J = 7.4$, 3.3 Hz), 4.23 (dd, 2H, 2H-9A, $^2J = 10.3$ Hz, $^3J = 7.4$ Hz), 4.78 (dd, 2H, 2 H-7, $^3J = 7.0$, 2.4 Hz), 4.79 (t, 2H, 2H-14, $^3J = 6.4$ Hz), 5.24 (ddd, 2H, 2H-3, $^3J = 7.7$, 4.9, 4.2 Hz), 7.13 (d, 2H, 2 NH lactam, $^3J = 7.7$ Hz), 7.28–7.40 (m, 24H, 24 Ar-H). ^{13}C NMR and HSQC (100 MHz, CDCl_3) δ_{C} 31.6 (2C-13), 41.3 (2C-6), 45.4 (2C-12), 52.4 (2CH₃), 52.4 (2C-3), 54.1 (2 OCH₃), 54.2 (2C-15), 62.8 (2C-10), 67.3 (2C-9), 69.7 (2C-2), 101.7 (2C-7), 102.2 (2C-14), 127.0–128.9 (24 Ar-CH), 138.3 (2 Ar-C), 138.5 (2 Ar-C), 139.6 (2 Ar-C), 168.7 (2CO). MS (ESI⁺): m/z (%) 981 (23) $[\text{M} + \text{Na}]^+$, 959 (100) $[\text{M} + \text{H}]^+$, 613 (14), 499 (23), 491 (10). HRMS (ESI⁺): calcd. for $\text{C}_{56}\text{H}_{71}\text{N}_4\text{O}_{10}$ $[\text{M} + \text{H}]^+$ 959.5170, found 959.5214.

Data for **16c**: $R_f = 0.66$ (Et₂O/MeOH, 98:2). $[\alpha]_{\text{D}}^{20} -77.2$ (c 0.23, CHCl_3). IR (CHCl_3): ν_{max} 3435 and 3360 (NH), 1666 (CO). ^1H NMR and COSY ^1H - ^1H (400 MHz, CDCl_3): δ_{H} 1.85 (m, 2H, H-13A, H-13B), 2.60 (dd, 1H, H-6B, $^2J = 14.6$ Hz, $^3J = 2.6$ Hz), 2.66 (dd, 1H, H-6A, $^2J = 14.6$ Hz, $^3J = 6.8$ Hz), 2.74 (ddd, 1H, H-12B, $^2J = 13.3$ Hz, $^3J = 6.8$, 5.7 Hz), 3.15 (ddd, 1H, H-12A, $^2J = 13.3$ Hz, $^3J = 7.5$, 5.6 Hz), 3.18 (s, 3H, OCH₃), 3.24 (s, 3H, OCH₃), 3.45 (d, 1H, H-15B, $^2J = 14.7$ Hz), 3.74 (d, 1H, H-15A, $^2J = 14.7$ Hz), 3.79 (dd, 1H, H-9B, $^2J = 10.5$ Hz, $^3J = 2.9$ Hz), 3.83 (dd, H, H-2B, $^2J = 10.7$ Hz, $^3J = 3.6$ Hz), 3.91 (dd, 1H, H-10, $^3J = 7.7$, 2.9 Hz), 3.92 (dd, 1H, H-2A, $^2J = 10.7$ Hz, $^3J = 4.9$ Hz), 4.25 (dd, 1H, H-9A, $^2J = 10.5$ Hz, $^3J = 7.7$ Hz), 4.51 (s, 2H, CH₂Br), 4.77 (dd, 1H, H-14, $^3J = 6.6$, 4.0 Hz), 4.78 (dd, 1H, H-7, $^3J = 6.8$, 2.6 Hz), 5.24 (ddd, 1H, H-3, $^3J = 7.7$, 4.9, 3.6 Hz), 7.15 (d, 1H, NH lactam, $^3J = 7.7$ Hz), 7.28–7.40 (m, 14H, 14 Ar-H). ^{13}C NMR and HSQC (100 MHz, CDCl_3), HMBC (125 MHz, CDCl_3): δ 31.7 (C-

13), 33.7 (CH₂Br), 41.2 (C-6), 45.3 (C-12), 52.5 (C-3), 52.6 (OCH₃), 54.2 (C-15), 53.3 (OCH₃), 63.1 (C-10), 67.3 (C-9), 69.8 (C-2), 101.8 (C-7), 102.2 (C-14), 127.0–129.2 (14 Ar-CH), 136.4 (Ar-C), 138.0 (Ar-C), 139.6 (Ar-C), 140.6 (Ar-C), 168.6 (CO). MS (ESI⁺): *m/z* (%) = 635 (29) [M + Na (⁸¹Br)]⁺, 633 (28) [M + Na (⁷⁹Br)]⁺, 613 (100) [M + H (⁸¹Br)]⁺, 611 (98) [M + H (⁷⁹Br)]⁺. HRMS (ESI⁺): calcd. for C₃₂H₄₀⁷⁹BrN₂O₅ [M + H]⁺ 611.2121, found 611.2131.

6.1.3.3. Bis-(3*S*,7*S*,10*S*,14*R*)-dimethyl diketal aminolactam (14b) and (3*S*,7*S*,10*S*,14*R*)-bromoxyl dimethyl diketal aminolactam (17b)

These compounds were prepared from dimethyl diketal aminolactam **5b** (15.2 mg, 50.0 μmol), α,α'-dibromo-*p*-xylene (7.9 mg, 30.0 μmol, 0.6 equiv.), K₂CO₃ (8.3 mg, 60.0 μmol, 1.2 equiv.), and CH₃CN (1.0 mL, *c*_{substrate} = 50 × 10⁻³ M) according to the general procedure (reaction time 9 h). Chromatography (Et₂O/MeOH, gradient 100:0–50:50) afforded bis-dimethyl diketal aminolactam **14b** (11.5 mg, 16.2 μmol, 72%) and bromoxyl dimethyl diketal aminolactam **17b** (1.3 mg, 2.7 μmol, 6%) with 90% conversion rate.

Data for **14b**: *R*_f = 0.35 (Et₂O/MeOH, 50:50), 0.45 (MeOH/NH₄OH, 99:1). [α]_D²⁵ + 55.2 (*c* 0.69, CHCl₃). IR (CHCl₃): ν 3365 (NH), 1653 (CO). ¹H NMR, COSY ¹H-¹H (400 MHz, CDCl₃): δ_H 1.02 (d, 6H, 2CH₃, ³*J* = 6.9 Hz), 1.24 (d, 6H, 2CH₃, ³*J* = 6.7 Hz), 1.86 (m, 4H, 4H-13), 2.49 (dd, 2H, 2H-6B, ²*J* = 16.8 Hz, ³*J* = 1.9 Hz), 2.53 (dt, 2H, 2H-12B, ²*J* = 12.5 Hz, ³*J* = 3.9 Hz), 2.72 (dd, 2H, 2H-6A, ²*J* = 16.8 Hz, ³*J* = 9.0 Hz), 2.90 (qdd, 2H, 2H-10, ³*J* = 6.9, 6.3, 2.2 Hz), 3.16 (ddd, 2H, 2H-12A, ²*J* = 12.5 Hz, ³*J* = 11.5, 5.1 Hz), 3.27 (s, 6H, 2 OCH₃), 3.32 (s, 6H, 2 OCH₃), 3.35 (d, 2H, 2H-15B, ²*J* = 14.3 Hz), 3.45 (dd, 2H, 2H-2B, ²*J* = 9.7 Hz, ³*J* = 3.1 Hz), 3.54 (ABX system, AB part, 4H, 2H-9A, 2H-9B, ²*J* = 10.0 Hz, ³*J* = 6.3, 2.2 Hz, Δ*v* = 13.4 Hz), 3.76 (dd, 2H, 2H-2A, ²*J* = 9.7 Hz, ³*J* = 2.0 Hz), 3.81 (d, 2H, 2H-15A, ²*J* = 14.3 Hz), 4.27 (m, 2H, 2H-3), 4.73 (dd, 2H, 2H-7, ³*J* = 9.0, 1.9 Hz), 4.81 (dd, 2H, 2H-14, ³*J* = 8.7, 2.6 Hz), 7.26 (d, 4H, 4 ArH, ³*J* = 7.1 Hz), 7.48 (d, 1H, NH lactam, ³*J* = 8.6 Hz). ¹³C NMR and HSQC (100 MHz, CDCl₃): δ_C 8.0 (2CH₃), 18.1 (2CH₃), 30.8 (2C-13), 39.4 (2C-6), 44.4 (2C-12), 44.6 (2C-3), 51.9 (2 OCH₃), 53.8 (2C-10), 53.9 (2C-15), 54.4 (2 OCH₃), 67.8 (2C-9), 71.4 (2C-2), 99.7 (2C-7), 102.3 (2C-14), 128.4 (4 Ar-CH), 138.8 (2 Ar-C), 167.9 (2CO). MS (APCI⁺) *m/z* (%) 711 (100) [MH]⁺, 679 (30) [M + H-CH₃OH]⁺, 647 (7). HRMS (ESI⁺): calcd. for C₃₆H₆₃N₄O₁₀ [M + H]⁺ 711.4544, found 711.4576.

Data for **17b**: *R*_f = 0.55 (Et₂O/MeOH, 50:50), 0.75 (MeOH/NH₄OH, 99:1). [α]_D²⁵ + 19.0 (*c* 0.65, CHCl₃). IR (CHCl₃): ν_{max} 3365 and 3290 (NH), 1662 (CO). ¹H NMR and COSY ¹H-¹H (400 MHz, CDCl₃): δ_H 1.02 (d, 3H, CH₃, ³*J* = 6.8 Hz), 1.25 (d, 3H, CH₃, ³*J* = 6.8 Hz), 1.84 (m, 2H, H-13A, H-13B), 2.50 (dd, 1H, H-6B, ²*J* = 16.6 Hz, ³*J* = 1.9 Hz), 2.54 (dt, 1H, H-12B, ²*J* = 12.5 Hz, ³*J* = 4.1 Hz), 2.73 (dd, 1H, H-6A, ²*J* = 16.6 Hz, ³*J* = 9.0 Hz), 2.92 (dq, 1H, H-10, ³*J* = 6.8, 6.0, 2.0 Hz), 3.15 (ddd, 1H, H-12A, ²*J* = 12.5 Hz, ³*J* = 11.0, 6.1 Hz), 3.25 (s, 3H, OCH₃), 3.31 (s, 3H, OCH₃), 3.41 (d, 1H, H-15B, ²*J* = 14.7 Hz), 3.44 (dd, 1H, H-2B, ²*J* = 10.0 Hz, ³*J* = 2.8 Hz), 3.55 (ABX, AB part, 2H, H-9A, H-9B, ²*J* = 10.0, ³*J* = 6.0, 2.0 Hz, Δ*v* = 11.1 Hz), 3.75 (dd, 1H, H-2A, ²*J* = 10.0 Hz, ³*J* = 1.8 Hz), 3.81 (d, 1H, H-15A, ²*J* = 14.7 Hz), 4.26 (m, 1H, H-3), 4.50 (s, 2H, CH₂Br), 4.71 (dd, 1H, H-7, ³*J* = 9.0, 1.9 Hz), 4.75 (dd, 1H, H-14, ³*J* = 7.8, 3.2 Hz), 7.26 (d, 4H, 4 Ar-H, ³*J* = 7.1 Hz), 7.46 (d, 1H, NH lactam, ³*J* = 8.1 Hz). ¹³C NMR and HSQC (100 MHz, CDCl₃) δ_C 8.1 (CH₃), 18.1 (CH₃), 30.9 (C-13), 33.6 (CH₂Br), 39.5 (C-6), 44.3 (C-12), 44.5 (C-3), 52.0 (OCH₃), 53.0 (C-10), 54.0 (C-15), 54.3 (OCH₃), 67.7 (C-2), 71.4 (C-9), 99.7 (C-7), 102.3 (C-14), 128.5–129.2 (4 Ar-CH), 137.1 (Ar-C), 145.0 (Ar-C), 168.0 (CO). MS (APCI⁺): *m/z* (%) 489 (92) [M + H (⁸¹Br)]⁺, 487 (79) [M + H (⁷⁹Br)]⁺, 457 (57) [M + H-CH₃OH (⁸¹Br)]⁺, 455 (36) [M + H-CH₃OH (⁷⁹Br)]⁺, 431 (100), 429 (91), 385 (15), 127 (49). HRMS (ESI⁺): calcd for C₂₂H₃₆⁷⁹BrN₂O₅ [M + H]⁺ 487.1807, found 487.1826.

6.1.3.4. Bis-(7*S**,14*R**)-diketal aminolactam (15b)

This compound was prepared from diketal aminolactam **6b** (13.8 mg, 50.0 μmol), α,α'-dibromo-*p*-xylene (6.6 mg, 25.0 μmol, 0.5 equiv.), K₂CO₃ (6.9 mg, 50.0 μmol, 1.0 equiv.), and CH₃CN (1.0 mL, *c*_{substrate} = 50 × 10⁻³ M) according to the general procedure (reaction time 9 h). Chromatography (Et₂O/MeOH, gradient 100:0–0:100) afforded bis-diketal aminolactam **15b** (6.6 mg, 10.1 μmol, 48%) with 84% conversion rate. *R*_f = 0.38 (MeOH/NH₄OH, 99:1). IR (CHCl₃): ν_{max} 3450 and 3369 (NH), 1656 (CO). ¹H NMR and COSY ¹H-¹H (400 MHz, CDCl₃): δ_H 1.91 (m, 4H, 4H-13), 2.48 (m, 2H, 2H-10B), 2.52 (dd, 2H, 2H-6B, ²*J* = 15.1 Hz, ³*J* = 1.0 Hz), 2.58 (m, 2H, 2H-12B), 2.66 (dd, 2H, 2H-6A,

$^2J = 15.1$ Hz, $^3J = 7.8$ Hz), 2.68 (m, 2H, 2H-10A), 2.88 (m, 2H, 2H-12A), 3.30 (s, 6H, 2 OCH₃), 3.31 (s, 6H, 2 OCH₃), 3.42 (d, 2H, 2H-15B, $^2J = 15.0$ Hz), 3.50 (m, 4H, 4H-3), 3.51 (m, 2H, 2H-2B), 3.57 (ddd, 2H, 2H-9B, $^2J = 9.0$ Hz, $^3J = 8.4$, 1.0 Hz), 3.70 (d, 2H, 2H-15A, $^2J = 15.0$ Hz), 3.73 (m, 2H, 2H-9A), 3.78 (m, 2H, 2H-2A), 4.70 (dd, 2H, 2H-7, $^3J = 7.8$, 1.0 Hz), 4.73 (dd, 2H, 2H-14, $^3J = 10.4$, 5.2 Hz), 7.25 (br. s, 2H, 2 NH lactam), 7.26 (d, 4H, 4 Ar-H, $^3J = 7.8$ Hz). ¹³C NMR and HSQC (100 MHz, CDCl₃): δ_C 30.2 (2C-13), 38.8 (2C-3), 40.5 (2C-6), 49.9 (2C-12), 52.5 (2 OCH₃), 53.4 (2 OCH₃), 54.0 (2C-10), 57.9 (2C-15), 64.7 (2C-2), 65.2 (2C-9), 100.4 (2C-7), 101.4 (2C-14), 129.0 (4 Ar-CH), 140.3 (2 Ar-C), 169.0 (2CO). MS (ESI⁺): m/z (%) 693 (5) [M + K]⁺, 677 (76) [M + Na]⁺, 655 (100) [M + H]⁺, 623 (4) [M + H-CH₃OH]⁺. HRMS (ESI⁺): calcd. for C₃₂H₅₅N₄O₁₀ [M + H]⁺ 655.3918, found 655.3931.

6.1.3.5. Bis-(7*R**,14*R**)-diketal aminolactam (15c)

This compound was prepared from diketal aminolactam **6c** (16.6 mg, 60.0 μ mol), α,α' -dibromo-*p*-xylene (9.5 mg, 36.0 μ mol, 0.6 equiv.), K₂CO₃ (10.0 mg, 72.0 μ mol, 1.2 equiv.), and CH₃CN (1.2 mL, $c_{\text{substrate}} = 50 \times 10^{-3}$ M) according to the general procedure (reaction time 9 h). Chromatography (Et₂O/MeOH, gradient 100:0–0:100) afforded bis-diketal aminolactam **15c** (9.4 mg, 14.3 μ mol, 55%) with 87% conversion rate. $R_f = 0.35$ (MeOH). IR (CHCl₃): ν_{max} 3450 and 3350 (NH), 1660 (CO). ¹H NMR and COSY ¹H-¹H (400 MHz, CDCl₃): δ_H 1.88 (m, 4H, 4H-13), 2.53 (m, 6H, 2H-6B, 2H-10B, 2H-12B), 2.64 (m, 4H, 2H-6A, 2H-10A), 2.90 (dt, 2H, 2H-12A, $^2J = 12.0$ Hz, $^3J = 6.0$ Hz), 3.21 (dddd, 2H, 2H-3B, $^2J = 11.2$ Hz, $^3J = 7.7$, 3.0, 1.0 Hz), 3.30 (s, 12H, 4 OCH₃), 3.40 (d, 2H, 2H-15B, $^2J = 14.0$ Hz), 3.50 (ddd, 2H, 2H-9B, $^2J = 8.1$ Hz, $^3J = 7.3$ Hz, 1.0 Hz), 3.57 (ddd, 2H, 2H-2B, $^2J = 9.0$ Hz, $^3J = 8.4$, 1.0 Hz), 3.72 (d, 2H, 2H-15A, $^2J = 14.0$ Hz), 3.76 (m, 4H, 2H-2A, 2H-9A), 3.81 (m, 2H, 2H-3A), 4.66 (dd, 2H, 2H-7, $^3J = 6.8$, 1.0 Hz), 4.72 (t, 2H, 2H-14, $^3J = 5.2$ Hz), 7.16 (br. s, 2H, 2 NH lactam), 7.26 (d, 4H, 4 ArH, $^3J = 8.0$ Hz). ¹³C NMR and HSQC (100 MHz, CDCl₃): δ_C 30.9 (2C-13), 39.2 (2C-3), 40.8 (2C-6), 50.2 (2C-12), 52.6 (2 OCH₃), 53.6 (2 OCH₃), 54.1 (2C-10), 58.2 (2C-15), 66.0 (2C-9, 2C-2), 100.9 (2C-7), 102.2 (2C-14), 129.1 (4 Ar-CH), 140.2 (2C-16), 169.1 (2CO). MS (ESI⁺): m/z (%) 693 (19) [M + K]⁺, 677 (8) [M + Na]⁺, 655 (100) [M + H]⁺, 627 (4) [M + H-CH₃OH]⁺. HRMS (ESI⁺): calcd. for C₃₂H₅₅N₄O₁₀ [M + H]⁺ 655.3918, found 655.3887.

6.1.4. Bis-diketal diamines: general procedure

To a solution of bis-diketal aminolactam (1 equiv.) in dry THF ($c_{\text{substrate}} = 60 - 100 \times 10^{-3}$ M), was added, dropwise while stirring, a solution of LiAlH₄ (1 M solution in THF, 10 equiv.) and NEt₃ (0.02 equiv./LAH). The reaction mixture was heated at reflux for 6–9 h. Excess hydride was destroyed by adding H₂O (10 equiv./LAH). The precipitates were filtered and washed with THF and CH₂Cl₂. The organic layer was dried with MgSO₄ and evaporated in vacuo. Purification by flash chromatography (silicagel, Et₂O/MeOH and MeOH/NH₄OH) yielded bis-diketal diamines.

6.1.4.1. Bis-(3*S*,7*S*,10*S*,14*R*)-dimethyl diketal diamine (18b)

This compound was prepared from bis-dimethyl diketal aminolactam **14b** (11.4 mg, 16 μ mol), LiAlH₄ (1 M THF solution, 160 μ L, 160 μ mol, 10 equiv.), NEt₃ (1 M THF solution, 3.2 μ L, 3.2 μ mol, 0.02 equiv./LAH), THF (160 μ L, $c_{\text{substrate}} = 100 \times 10^{-3}$ M) according to the general procedure (reaction time 9 h). Excess hydride was destroyed by adding H₂O (29 μ L, 1.6 mmol). Chromatography (Et₂O/MeOH, gradient 100:0–0:100 and MeOH/NH₄OH, gradient 100:0–90:10) afforded bis-dimethyl diketal diamine **18b** (2.9 mg, 4.2 μ mol, 26%) and dimethyl diketal diamine **8b** (0.8 mg, 2.8 μ mol, 9%). Data for **18b**: $R_f = 0.20$ (MeOH/NH₄OH, 97:3). IR (CHCl₃): ν_{max} 3340 (NH). ¹H NMR and COSY ¹H-¹H (400 MHz, CDCl₃): δ_H 1.01 (d, 6H, 2CH₃, $^3J = 6.8$ Hz), 1.10 (d, 6H, 2CH₃, $^3J = 6.6$ Hz), 1.81 (m, 4H, 4H-13), 1.92 (m, 4H, 4H-6), 2.05 (br. s, 2H, 2 NH amine), 2.53 (dt, 2H, 2H-12B, $^2J = 12.5$ Hz, $^3J = 5.1$ Hz), 2.70 (m, 2H, 2H-5B), 2.90 (m, 6H, 2H-3, 2H-5A, 2H-10), 3.07 (ddd, 2H, 2H-12A, $^2J = 12.6$ Hz, $^3J = 9.5$, 6.2 Hz), 3.28 (s, 6H, 2 OCH₃), 3.32 (s, 6H, 2 OCH₃), 3.45 (d, 2H, 2H-15B, $^2J = 14.4$ Hz), 3.46 (dd, 2H, 2H-2B, $^2J = 10.0$ Hz, $^3J = 2.4$ Hz), 3.48 (td, 2H, 2H-9B, $^2J = 10.0$ Hz, $^3J = 6.0$ Hz), 3.61 (td, 2H, 2H-9A, $^2J = 10.0$ Hz, $^3J = 2.5$ Hz), 3.66 (dd, 2H, 2H-2A, $^2J = 10.0$ Hz, $^3J = 2.3$ Hz), 3.75 (d, 2H, 2H-15A, $^2J = 14.4$ Hz), 4.58 (dd, 2H, 2H-7, $^3J = 6.4$, 3.8 Hz), 4.77 (dd, 2H, 2H-14, $^3J = 7.1$, 1.8 Hz), 7.28 (d, 4H, 4 ArH, $^3J = 6.8$ Hz). ¹³C NMR and HSQC (100 MHz, CDCl₃), HMBC (125 MHz, CDCl₃): δ_C 9.7 (2CH₃),

16.0 (2CH₃), 32.0 (2C-6, 2C-13), 42.2 (2C-5), 44.4 (2C-12), 52.8 (2C-3), 52.9 (2 OCH₃), 54.3 (2 OCH₃), 54.5 (2C-10), 54.6 (2C-15), 68.3 (2C-2), 70.0 (2C-9), 101.8 (2C-14), 103.4 (2C-7), 128.3 (4 Ar-CH), 139.2 (2 Ar-C). MS (APCI) *m/z* (%): 705 (9) [M + Na]⁺, 683 (100) [M + H]⁺, 655 (7), 613 (8). HRMS (ESI⁺): calcd. for C₃₆H₆₇N₄O₈ [M + H]⁺ 683.4959, found 683.4955.

6.1.4.2. Bis-(7*R**,14*R**)-diketal diamine (**19c**)

This compound was prepared from bis-diketal aminolactam **15c** (10.5 mg, 16 μmol), LiAlH₄ (1 M THF solution, 160 μL, 160 μmol, 10 equiv.), NEt₃ (1 M THF solution, 3.2 μL, 3.2 μmol, 0.02 equiv./LAH), THF (267 μL, *c*_{substrate} = 60 × 10⁻³ M) according to the general procedure (reaction time 6 h). Excess hydride was destroyed by adding H₂O (29 μL, 1.6 mmol). Chromatography (Et₂O/MeOH, gradient 100:0–0:100 and MeOH/NH₄OH, gradient 100:0–70:30) afforded bis-diketal diamine **19c** (2.2 mg, 3.5 μmol, 22%) and diketal diamine **9c** (0.8 mg, 3.0 μmol, 9%).

Data for **19c**: *R*_f = 0.25 (MeOH/NH₄OH, 94:4, 2 elutions). IR (CHCl₃): *ν*_{max} 3300 (NH). NMR ¹H (400 MHz, CDCl₃): δ_H 1.70–2.10 (m, 14H, 2H-6B, 2H-13B, 2H-6A, 2H-13A, 2H-5B, 2H-12B, 2NH), 2.54 (m, 4H, 2H-3B, 2H-10B), 2.70 (m, 4H, 2H-3A, 2H-10A), 3.21 (d, 2H, 2H-15B, ²*J* = 14.5 Hz), 3.23 (m, 4H, 2H-5A, 2H-12A), 3.30 (s, 6H, 2 OCH₃), 3.38 (s, 6H, 2 OCH₃), 3.60–3.71 (m, 4H, 2H-2B, 2H-9B), 3.86–3.93 (m, 4H, 2H-2A, 2H-9A), 3.98 (d, 2H, 2H-15A, ²*J* = 14.5 Hz), 4.51 (ddd, 2H, 2H-7, ³*J* = 8.0, 4.7 Hz, ⁴*J* = 2.4 Hz), 4.58 (ddd, 2H, 2H-14, ³*J* = 7.4, 2.3 Hz, ⁴*J* = 1.7 Hz), 7.30 (d, 4H, 4 Ar-H, ³*J* = 6.6 Hz). ¹³C NMR (100 MHz, CDCl₃): δ_C 30.2 (2C-13), 31.7 (2C-6), 43.6 (2C-5), 47.4 (2C-3), 48.3 (2C-12), 52.5 (2C-10), 52.8 (2 OCH₃), 54.8 (2 OCH₃), 57.9 (2C-15), 63.3 (2C-2), 67.1 (2C-9), 102.4 (2C-14), 103.7 (2C-7), 129.7 (4 Ar-CH), 140.3 (2 Ar-C). MS (ESI⁺): *m/z* (%) 649 (40) [M + Na]⁺, 627 (100) [M + H]⁺. HRMS (ESI⁺): calcd. for [M + H]⁺ 627.4333, found 627.4329.

6.2. Biological assays

6.2.1. Anti-HIV activity

The cell cultures of MT-4 and CEM-SS cells were maintained at 37 °C in a 5% CO₂ atmosphere in RPMI 1640 medium supplemented with 10% foetal calf serum (FCS) containing penicillin, streptomycin and glutamine. MT-4 cells were infected with HIV-1_{IIIB} isolate at 5 TCID₅₀ (Tissue Culture Infective Dose) and CEM-SS cells with HIV-1 LAI isolate at 20 TCID₅₀. After 30 min of adsorption, the infected cells were washed to remove unadsorbed virus particles and resuspended in RPMI at the final concentration of 10⁵ cells/mL, in the presence of various dilutions of the test compounds. After 5 days, virus production was measured as already described [16]. The 50% inhibitory concentration (IC₅₀) was derived from the computer-generated median effect plot of the dose-effect data [17]. The cytotoxicity of the drugs was evaluated in parallel by incubating uninfected cells in the presence of ranging concentrations of anti-viral products. Cell viability was measured by means of a colorimetric reaction based on the capacity of mitochondrial dehydrogenase of living cells to reduce 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) into formazan, the quantity of which was determined by the optical density at 540 nm [18]. The 50% cytotoxic concentration (CC₅₀) was calculated with the program used for the determination of IC₅₀. The CEM-SS cells were obtained from P. Nara through the AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH.

6.2.2. Anti-tumoral activity

The cell cultures were maintained at 37 °C under 5% CO₂ atmosphere for 72 h, in either RPMI 1640 medium (cell lines: SF268, HL60, MCF7, MCF7R, HCT116, A549, PC3, OV3) or DMEM-Glutamax medium (cell lines: KB, HepG2), supplemented in both cases with 10% foetal calf serum (FCS) containing penicillin, streptomycin, fungizon and glutamine. Cells were plated at a density of 500–800 cells in 200 μL culture medium in each well of 96-well microplates and allowed to adhere for 24 h before treatment with test drugs in DMSO solution (final concentration: 10⁻⁵ M). Cell viability was assayed after 3 h drug exposure with tetrazolium compound [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2*H*-tetrazolium salt, MTS, Promega Corp.] using the Cell

Titer 96 Aqueous One Solution Cell Proliferation Assay kit (Promega Corp) according to the manufacturer's instructions. Absorbance was measured at 490 nm with a microplate reader.

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